Optimizing antiseizure medication treatment in glioma patients with epilepsy

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CHAPTER 5

Effectiveness of antiseizure medication duotherapies in patients with glioma: a multicenter observational cohort study

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Abstract

Background

About 30% of glioma patients need an add-on antiepileptic drug (AED) due to uncontrolled seizures on AED monotherapy. This study aimed to determine whether levetiracetam combined with valproic acid (LEV+VPA), a commonly prescribed duotherapy, is more effective than other duotherapy combinations including either LEV or VPA in glioma patients.

Methods

In this multicenter retrospective observational cohort study, treatment failure (i.e. replacement by, addition of, or withdrawal of an AED) for any reason was the primary outcome. Secondary outcomes included: 1) treatment failure due to uncontrolled seizures; and 2) treatment failure due to adverse effects. Time to treatment failure was estimated from moment of AED duotherapy initiation. Multivariable cause-specific cox proportional hazard models were estimated to study the association between risk factors and treatment failure. The maximum duration of follow-up was 36 months.

Results

A total of 1435 patients were treated with first-line monotherapy LEV or VPA, of which 355 patients received AED duotherapy after they had treatment failure due to uncontrolled seizures on monotherapy. LEV+VPA was prescribed in 66% (236/355) and other AED duotherapy combinations including LEV or VPA in 34% (119/355) of patients. Patients using other duotherapy versus LEV+VPA had higher risk of treatment failure for any reason (cause-specific adjusted hazard ratio [aHR]=1.50 [95%CI=1.07-2.12], p=0.020), due to uncontrolled seizures (cause-specific aHR=1.73 [95%CI=1.10-2.73], p=0.018), but not due to adverse effects (cause-specific aHR=0.88 [95%CI=0.47-1.67]), p=0.703).

Conclusions

This observational cohort study suggests that LEV+VPA has better efficacy than other AED combinations. Similar toxicities were experienced in the two groups.

Classification of evidence

This study provides Class III evidence that for glioma patients with uncontrolled seizures on AED monotherapy, LEV+VPA has better efficacy than other AED combinations.

Keywords

Glioma, brain tumor, valproic acid, levetiracetam, antiepileptic drug, seizure, treatment failure, retention rates

Introduction

Seizures occur frequently in glioma patients, with the preoperative seizure incidence in diffuse gliomas ranging from ~25% in World Health Organization (WHO) grade 4 glioblastoma IDH-wildtype to ~75% in grade 2 diffuse astrocytoma isocitrate dehydrogenase (IDH)-mutant and oligodendroglioma IDH-mutant 1p/19q codeleted patients.[1] Antiepileptic drugs (AEDs) are the cornerstone of anticonvulsant treatment, with levetiracetam (LEV) and valproic acid (VPA) being the most commonly prescribed AEDs in the glioma population.[2-4] Recently, it has been shown that first-line monotherapy with LEV has favorable efficacy over VPA, while having a similar level of toxicity.[5] In about 30% of glioma patients seizures are inadequately controlled by AED monotherapy and these patients generally need AED polytherapy treatment.[5] Preclinical evidence showed that especially the combination of LEV+VPA leads to a strong enhancement of anticonvulsant effects across different preclinical models and stood out compared to other AED combinations, suggesting a beneficial synergistic effect (i.e. an interaction effect between two drugs, resulting in a joint effect that is greater than the sum of the individual effects of each drug).[6] Among LEV's mechanism of action is modulation of synaptic neurotransmitter release through binding to the synaptic vesicle glycoprotein 2A in the brain,[7] indirectly affecting GABAergic neurotransmission as well.[8] VPA is regarded as having multiple mechanisms of action, including GABAergic potentiation, glutamate inhibition, and blockade of voltage-dependent sodium currents.[6, 9]

The International League Against Epilepsy (ILAE) recommends to use either an efficacy or effectiveness outcome as primary outcome in comparative AED studies.[10] The efficacy of an AED means its ability to achieve seizure freedom, while effectiveness includes both efficacy and tolerability, of which the latter encompasses the incidence, severity, and impact of AED-related adverse effects, which is most importantly reflected in AED discontinuation due to intolerable or life-threatening adverse reactions.[11] In two studies conducted in a large neuro-oncology outpatient clinic in the Netherlands, LEV+VPA was the most frequently prescribed and the most efficacious polytherapy combination in brain tumor patients.[12, 13] However, methodological issues such as the competing risk of death were not taken into account, hampering reliable interpretation of results.[11] Therefore, we investigated whether LEV+VPA had better effectiveness, efficacy, and/or tolerability compared to other AED duotherapy combinations, including LEV or VPA, in glioma patients with uncontrolled seizures on first-line monotherapy. Specifically, by estimating time to AED treatment failure for any reason, due to uncontrolled seizures, and due to adverse effects.

Methods

Study population and procedures

Details about the study cohort and methods have already been published elsewhere.[5] In short, the study population consisted of consecutive patients with a histologically diagnosed grade 2-4 glioma ([anaplastic] astrocytoma, [anaplastic] oligoastrocytoma, [anaplastic] oligodendroglioma, or glioblastoma) according to the World Health Organization (WHO) 2016 guidelines,[14] following biopsy or surgical (re)resection in Haaglanden Medical Center the Hague, Amsterdam University Medical Centers, or Erasmus Medical Center Rotterdam, between January 1st, 2004 and January 1st, 2018. In the original cohort, we included patients with epilepsy who received first-line monotherapy treatment with LEV or VPA. Regarding the current study, patients were included who showed treatment failure on either first-line LEV or VPA monotherapy due to uncontrolled seizures. Patients were excluded who: 1) were prescribed an add-on for a predetermined maximum term; 2) showed treatment failure on their first-line LEV or VPA due to other reasons than uncontrolled seizures; and 3) showed treatment failure due to uncontrolled seizures, but were treated with another AED as monotherapy. Incrementing AED dose and deciding whether addition of an AED due to uncontrolled seizures was warranted, was according to the judgement of the treating physician, taking into account the maximum daily dose according to national guidelines. This resulted in two groups which were compared: LEV+VPA versus other AED duotherapy including either LEV or VPA.

Patients' charts were examined to extract baseline sociodemographic and clinical characteristics, including radiological response data (i.e. tumor progression) according to the Response Assessment in Neuro-Oncology (RANO) criteria.[15] For this study, baseline was defined as the starting date of AED duotherapy initiation. Although LEV and VPA have equal defined daily dosages (DDD), this is not true for many other AEDs. Therefore, the AED load was calculated for each patient, defined as the sum of the ratio between the prescribed daily dosage and the DDD of each individual AED included in the AED treatment combination (eTable 1).[16]

Outcomes

The primary outcome was time to treatment failure for any reason from initiation of AED duotherapy, which is a measure for effectiveness of AED treatment and encompasses both AED efficacy and tolerability.[17] Treatment failure was defined as withdrawal, replacement, or the addition of an AED. The following conditions were not considered treatment failure: a change in the dosage of the initial AED combination, addition of an AED taken only as needed, addition of an AED with an indication other than seizures, use of a temporary prophylactic AED as add-on during a perioperative period, poor adherence less than one week, or replacement with a non-oral AED in the end-of-life phase due to swallowing

difficulties. Secondary outcomes: 1) time to treatment failure due to uncontrolled seizures from AED duotherapy initiation, as a measure of efficacy; 2) time to treatment failure due to adverse effects from AED duotherapy initiation, as a measure of tolerability; 3) time to recurrent epileptic seizure from AED duotherapy initiation, which is a measure for efficacy; and 4) level of toxicity, defined as severity (grade 1-5) of intolerable adverse effects leading to AED discontinuation according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0,[18] as a measure of tolerability. To determine how likely the intolerable adverse effect was attributable to the AED combination, it was evaluated whether the adverse effects improved or not, typically in a period of 1-2 months. If the adverse effects improved after AED discontinuation, the adverse effects were considered attributable to the AED combination,[19] if not this seemed less likely. Maximum duration of follow-up was 36 months. Patients were censored if they had not shown the event of interest and were still alive at 36 months or were lost to follow-up.

Statistics

Time to treatment failure and time to recurrent seizure of two AED duotherapy treatment groups (LEV+VPA versus other duotherapy including LEV or VPA) were compared, from the moment of AED duotherapy initiation. Multivariable Cox proportional hazard models were estimated to study the association between risk factor (i.e. AED duotherapy) and treatment failure. In case of an etiological research question (in contrast to prediction research) and the presence of competing risks, a Cox proportional hazards model is preferred and potential confounders should be selected on pre-existing knowledge.[11, 20] Four different competing risk models were estimated: 1) treatment failure for any reason (event of interest) versus death; 2) treatment failure due to uncontrolled seizures (event of interest) versus treatment failure due to other reasons than uncontrolled seizures and death; 3) treatment failure due to adverse effects (event of interest) versus treatment failure due to other reasons than adverse effects and death; and 4) recurrent seizure (event of interest) versus treatment failure before a recurrent seizure has occurred and death.[21] All Cox models were repeated for subgroup analyses within the other duotherapy group with the same potential confounders, the AED combinations with the LEV group was compared with the VPA group. The proportional hazards assumption was checked by considering Schoenfeld residuals, nonlinearity by Martingale residuals, and influential observations by deviance residuals. The censoring distribution was checked by modelling time to censoring in the same way as time to any event of interest. In the censoring model, the event of interest was censoring. Therefore, patients who were lost to follow-up had an 'event'. Patients that were not censored (i.e. those who experienced the original event of interest) were now considered censored, since their censoring time was not observed. In our study all baseline covariates, which were significant for the time to the event of interest, were included in the model. To assess the difference between the cumulative incidences, the Gray test was used.[22] Presence

of radiological tumor progression at time of treatment failure due to uncontrolled seizures, presence of residual tumor at baseline, severity of intolerable adverse effects (grade 1/2 versus 3/4) in patients using LEV+VPA versus other AED duotherapy, and whether or not adverse effects improved were compared using the χ^2, while dosage at moment of treatment failure was analysed using the independent t-test. The following potential confounding variables were considered in each analysis, and were considered to be relevant for the outcome as based on previous literature and expert opinion: age, sex, tumor grade, IDH-mutation status, surgical resection, radiotherapy, systemic therapy, tumor location, Karnofsky Performance Status, history of psychiatric disorder (depression, anxiety, or psychotic disorder), and seizure type. Median follow-up time (including interquartile range [IQR]) was calculated with the reverse Kaplan Meier' methodology. Statistical analyses were performed using statistical packages *SPSS* version 25.0 and *R*, an open software environment.[23, 24] All analyses concerning the competing risks models were performed in R with the cmprsk library.[21] A p-value of <0.05 was considered statistically significant.

Standard protocol approvals, registrations, and patient consents

The medical ethics committee of each institution approved the protocol and consent of patients was obtained according to the institutions policy.

Data availability

Data are available upon reasonable request.

Results

Patient characteristics

Baseline cohort characteristics of patients on AED duotherapy are reported in Table 1. The original study population consisted of 1435 patients prescribed first-line monotherapy LEV or VPA. A total of 382 unique patients experienced treatment failure due to uncontrolled seizures on their first-line AED, of which 7% (27/382) started with another AED as monotherapy and 93% (355/382) patients started with AED duotherapy (Figure 1). LEV+VPA was prescribed to 236 (236/355=66%) and other AED duotherapy including LEV or VPA to 119 (119/355=34%) patients (Table 2). Other AED duotherapy consisted of 15 unique combinations, of which 68 patients used a combination with VPA and 51 with LEV. LEV+clobazam (19/119=16%) and VPA+phenytoin (18/119=15%) were prescribed most commonly as other AED duotherapy. At baseline 62% (147/236) of patients in the LEV+VPA group had received surgical resection and 49% (58/119) of patients in the other AED duotherapy group. Presence of residual tumor did not differ significantly between LEV+VPA and other AED duotherapy (73% [108/147] versus 79% [46/58] subtotal resection, p=0.384). Median follow-up time was 16 months (IQR=5-36 months).

Table 1. Demographic characteristics of the patients at baseline of antiepileptic drug duotherapy.

Characteristics	Antiepileptic drug treatment	
	LEV+VPA	Other duotherapy
Patients included, no.	236	119
Age, mean (SD)	52 (14)	45 (13)
Sex, no. (%)		
Male	165 (70)	71 (60)
Female	71 (30)	48 (40)
Tumor grade and pathology, no. (%)		
Grade 2	65 (28)	41 (34)
Diffuse astrocytoma NOS	24 (10)	17 (14)
Diffuse astrocytoma IDH-mutant	13 (6)	8 (7)
Oligodendroglioma NOS	12 (5)	5 (4)
Oligodendroglioma IDH-mutant 1p/19q codeletion	12 (5)	10 (8)
Oligoastrocytoma NOS	4 (2)	1 (1)
Grade 3	27 (11)	23 (19)
Anaplastic astrocytoma NOS	18 (8)	10 (8)
Anaplastic astrocytoma IDH-mutant	1 (0)	2 (2)
Anaplastic oligodendroglioma NOS	5 (2)	6 (5)
Anaplastic oligodendroglioma IDH-mutant 1p/19q codeletion	3 (1)	4 (3)
Anaplastic oligoastrocytoma NOS	0 (0	1 (1)
Grade 4	144 (61)	55 (46)
Diffuse astrocytoma wildtype	3 (1)	3 (3)
Anaplastic astrocytoma wildtype	2 (1)	3 (3)
Glioblastoma NOS	123 (52)	32 (27)
Glioblastoma wildtype	15 (6)	14 (12)
Glioblastoma IDH-mutant	1 (0)	3 (3)
Surgical resection, no. (%)		
Gross total resection, no. (%)	39 (17)	12 (10)
Subtotal resection, no. (%)	108 (46)	46 (39)
Biopsy, no. (%)	46 (19)	22 (18)
No resection or biopsy, no. (%)	43 (18)	39 (33)
Radiotherapy, no. (%)		
Yes	123 (52)	54 (45)
No	113 (48)	65 (55)
Systemic therapy, no. (%)		
Yes	101 (43)	41 (34)
Temozolomide (+ additional agents)	97 (41)	39 (33)
Temozolomide rechallenge (+ additional agents)	4 (2)	1 (1)
PCV[a] (+ additional agents)	6 (3)	5 (4)
Lomustine (+ additional agents)	7 (3)	9 (8)
Other	3 (1)	0 (0)
No	135 (57)	78 (66)
Tumor involvement in the temporal lobe		
Yes	96 (41)	54 (45)
No	140 (59)	65 (55)

Table 1. Continued

Characteristics	Antiepileptic drug treatment	
	LEV+VPA	Other duotherapy
Tumor involvement in the frontal lobe		
Yes	150 (64)	84 (71)
No	86 (36)	35 (29)
Karnofsky Performance Status, no. (%)		
≥70	198 (84)	109 (92)
<70	38 (16)	10 (8)
History of a psychiatric disease[b], no. (%)		
Yes	14 (6)	8 (7)
No	222 (94)	111 (93)
Seizure type, no. (%)		
Focal	82 (35)	36 (30)
Focal to bilateral tonic-clonic[c]	154 (65)	83 (70)

[a]PCV=Procarbazine, Lomustine, and Vincristine; [b]History of a psychiatric disease included depression, anxiety, or psychotic disorders; [c]Patients had either solely focal to bilateral tonic-clonic seizures or both focal and focal to bilateral tonic-clonic seizures; LEV+VPA=Levetiracetam combined with valproic acid; No.=Number of patients; SD=Standard deviation

Time to treatment failure

A total of 42% (99/236) of patients who used the combination of LEV+VPA showed treatment failure within 36 months follow-up, versus 55% (65/119) of patients who used AED duotherapy with either LEV or VPA combined with another AED. Main reason of treatment failure for LEV+VPA and other AED duotherapy was uncontrolled seizures (23% [55/236] versus 31% [37/119] patients), followed by adverse effects (15% [35/236] versus 13% [15/119] patients), other reasons (3% [7/236] versus 7% [8/119] patients), and withdrawal due to remission of seizures (1% [2/236] versus 4% [5/119] patients). The cumulative incidence of treatment failure for any reason of LEV+VPA and other AED duotherapy at 12 months were 37% (95%CI=30-43%) versus 50% (95%CI=40-59% [eTable 2]). The cumulative incidence of LEV+VPA versus other AED duotherapy at 12 months for treatment failure due to uncontrolled seizures was 21% (95%CI=16-26) versus 29% (95%CI=21-38%), and for treatment failure due to adverse effects was 13% (95%CI=9-18%) versus 11% (95%CI=6-18%), respectively (eTable 3). Other AED duotherapy had a significantly higher risk of treatment failure for any reason compared to the combination of LEV+VPA (cause-specific adjusted hazard ratio [aHR]=1.50 [95%CI=1.07-2.12], p=0.020 [Table 3]). With regard to specific reasons of treatment failure, patients using other AED duotherapy were more likely to experience treatment failure due to uncontrolled seizures (cause-specific aHR=1.73 [95%CI=1.10-2.73], p=0.018 [eTable 4]), but not treatment failure due to adverse effects (cause-specific aHR=0.88 [95%CI=0.47-1.67], p=0.703 [eTable 5]).

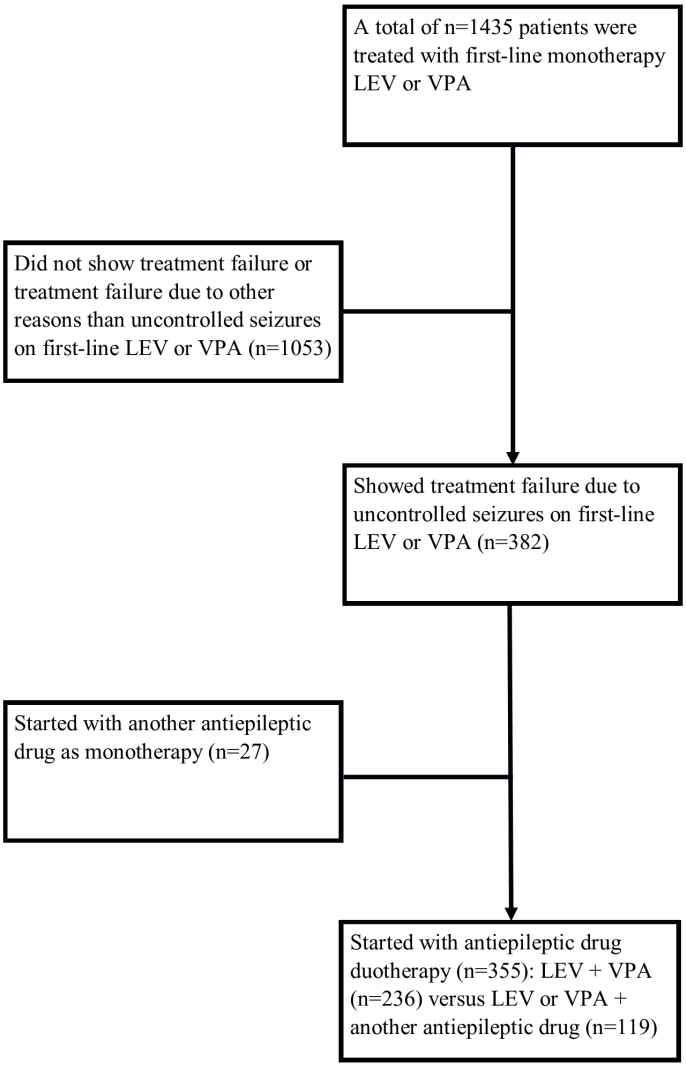

Figure 1. Flow diagram of in- and excluded patients

Mean AED load at moment of treatment failure in patients on LEV+VPA and other AED duotherapy was similar for those showing treatment failure due to uncontrolled seizures (2.44 [SD=0.58] versus 2.30 [SD=0.61] AED load, p=0.276) or intolerable adverse effects (2.03 [SD=0.46] versus 1.84 [SD=0.39] AED load, p=0.215). Tumor progression at time of treatment failure due to uncontrolled seizures did not differ significantly between LEV+VPA and other AED duotherapy (45% [25/55] versus 38% [14/37], p=0.469).

Table 2. Antiepileptic drug duotherapy in detail.

Characteristics antiepileptic drug duotherapy	Number of patients (%)
Patients included	355 (100)
Levetiracetam + valproic acid	236 (66)
Other duotherapy	119 (34)
Levetiracetam + carbamazepine	5 (1)
Levetiracetam + clobazam	19 (5)
Levetiracetam + clonazepam	1 (0)
Levetiracetam + lacosamide	13 (4)
Levetiracetam + lamotrigine	5 (1)
Levetiracetam + phenytoin	7 (2)
Levetiracetam + topiramate	1 (0)
Valproic acid + carbamazepine	15 (4)
Valproic acid + clobazam	15 (4)
Valproic acid + gabapentin	1 (0)
Valproic acid + lacosamide	4 (1)
Valproic acid + lamotrigine	5 (1)
Valproic acid + oxcarbamazepine	2 (1)
Valproic acid + phenytoin	18 (5)
Valproic acid + topiramate	8 (2)

Time to recurrent seizure

A recurrent seizure within 36 months follow-up occurred in 78% (182/232) patients on LEV+VPA versus 85% (99/116) on other AED duotherapy combinations. The cumulative incidence of recurrent seizure at 12 months was 74% (95%CI=68-79%) for LEV+VPA and 87% (95%CI=79-92%) for other AED duotherapies (eTable 6). Patients in the other AED duotherapy group had a significantly higher risk of having a recurrent seizure (cause-specific aHR=1.66 [95%CI=1.28-2.17], p<0.001 [Table 4]).

Intolerable adverse effects leading to treatment failure

A total of 47 adverse effects were reported in the LEV+VPA group that led to treatment failure, occurring in 15% (35/236) of patients. Similarly, 24 adverse effects leading to treatment failure were reported in 13% (15/119) of patients in the other AED duotherapy group (Table 5). Hepatobiliary disorders occurred only in the LEV+VPA group (2/47=4%) and were transient in half of these cases (1/2=50%). Psychiatric disorders occurred in 17% (8/47) of patients in the LEV+VPA group and improved in almost all (7/8=88%), while psychiatric disorders occurred in 8% (2/24) of patients in the other AED duotherapy group and improved in none (0/2=0%). The two most common intolerable adverse effects for the

Table 3. Unadjusted and adjusted cause-specific hazard ratios of time to treatment failure for any reason.

		Treatment failure for any reason			
Parameter[a]		**uHR (95% CI)**	**p-value**	**aHR (95% CI)**	**p-value**
AED treatment	LEV+VPA (ref.)				
	Other duotherapy	1.47 (1.07-2.01)	0.016*	1.50 (1.07-2.12)	0.020*
Age		1.00 (0.99-1.01)	0.989	1.00 (0.99-1.02)	0.977
Sex	Male (ref.)				
	Female	1.04 (0.75-1.44)	0.835	1.05 (0.75-1.48)	0.780
Tumor grade	2 (ref.)				
	3	0.91 (0.57-1.43)	0.669	1.11 (0.67-1.84)	0.697
	4	1.10 (0.78-1.56)	0.573	1.34 (0.83-2.18)	0.234
Surgical resection	No (including biopsy, ref.)				
	Yes	0.94 (0.69-1.28)	0.707	1.02 (0.73-1.44)	0.892
Tumor involvement in the temporal lobe	No (ref.)				
	Yes	0.93 (0.68-1.27)	0.627	0.96 (0.69-1.34)	0.802
Tumor involvement in the frontal lobe	No (ref.)				
	Yes	1.05 (0.75-1.48)	0.763	0.88 (0.61-1.29)	0.519
Karnofsky Performance Status	≥70 (ref.)				
	<70	1.03 (0.52-2.05)	0.937	0.99 (0.48-2.03)	0.972
History of a psychiatric disease[b]	No (ref.)				
	Yes	1.47 (0.86-2.50)	0.156	1.51 (0.87-2.63)	0.143
Seizure type	Focal (ref.)				
	Focal to bilateral tonic clonic[c]	1.15 (0.82-1.62)	0.411	1.14 (0.80-1.63)	0.463

[a]Isocitrate dehydrogenase (IDH)-mutation, radiotherapy, and systemic therapy did not hold the proportionality assumption of the Cox regression model and were therefore stratified; [b]History of a psychiatric disease included depression, anxiety, or psychotic disorders; [c]Patients had either solely focal to bilateral tonic-clonic seizures or both focal and focal to bilateral tonic-clonic seizures; *P-value <0.05; AED=Antiepileptic drug; aHR=Adjusted hazard ratio; CI=Confidence interval; LEV+VPA=Levetiracetam combined with valproic acid; ref.=Reference; uHR=Unadjusted hazard ratio

combination of LEV+VPA were tremor (8/47=17%) and decreased platelet count (4/47=9%), and for the other AED duotherapies this was somnolence (3/24=13%) and rash (3/24=13% [eTable 7]). Only a small number of adverse effects in the LEV+VPA and the other AED duotherapy group were grade 3 or 4 (23% [11/47] versus 21% [5/24], p=0.389) or did not improve after discontinuation of an AED (11% [5/47] versus 21% [5/24], p=0.464).

Subgroup analyses within the other duotherapy group

Within the other AED duotherapy group, 68 patients were on a combination with VPA and

Table 4. Unadjusted and adjusted cause-specific hazard ratios of time to recurrent seizure

		Recurrent seizure			
Parameter		**uHR (95% CI)**	**p-value**	**aHR (95% CI)**	**p-value**
AED treatment	LEV+VPA (ref.)				
	Other duotherapy	1.63 (1.27-2.09)	<0.001*	1.66 (1.28-2.17)	<0.001*
Age		1.00 (0.99-1.00)	0.328	1.00 (0.99-1.01)	0.731
Tumor grade	2 (ref.)				
	3	0.78 (0.53-1.13)	0.190	0.81 (0.55-1.20)	0.297
	4	0.93 (0.71-1.20)	0.564	0.95 (0.66-1.36)	0.776
Isocitrate dehydrogenase (IDH)-mutation	No (ref.)				
	Yes	1.03 (0.75-1.40)	0.873	0.89 (0.62-1.28)	0.527
Surgical resection	No (including biopsy, ref.)				
	Yes	0.82 (0.65-1.03)	0.091	0.85 (0.66-1.11)	0.232
Radiotherapy	No (ref.)				
	Yes	0.83 (0.65-1.05)	0.113	0.60 (0.41-0.89)	0.011*
Systemic therapy	No (ref.)				
	Yes	1.09 (0.86-1.38)	0.489	1.66 (1.11-2.48)	0.014*
Tumor involvement in the temporal lobe	No (ref.)				
	Yes	1.17 (0.92-1.48)	0.191	1.16 (0.91-1.47)	0.236
Karnofsky Performance Status	≥70 (ref.)				
	<70	1.21 (0.82-1.78)	0.334	1.31 (0.87-1.97)	0.194
Seizure type	Focal (ref.)				
	Focal to bilateral tonic clonic[a]	0.85 (0.66-1.09)	0.197	0.81 (0.62-1.04)	0.099

[a]Patients had either solely focal to bilateral tonic-clonic seizures or both focal and focal to bilateral tonic-clonic seizures; *P-value <0.05; AED=Antiepileptic drug; aHR=Adjusted hazard ratio; CI=Confidence interval; LEV+VPA=Levetiracetam combined with valproic acid; ref.=Reference; uHR=Unadjusted hazard ratio

51 patients on a combination with LEV. Treatment failure rates for the combinations with VPA and the combinations with LEV were as follows: treatment failure for any reason was 57% (39/68) versus 51% (26/51), treatment failure due to uncontrolled seizures was 27% [19/68] versus 35% [18/51], and treatment failure due to adverse effects was 21% [14/68] versus 2% [1/51], respectively. The percentages of a recurrent seizure for patients on combinations with VPA versus combinations with LEV was 85% [55/65] versus 86% [44/51]. There was no significant difference in the risk of having treatment failure for any reason when combinations with VPA was compared to combinations with LEV (cause-specific aHR=1.32 [95%CI=0.75-2.31], p=0.331), for treatment failure due to uncontrolled seizures (cause-specific aHR=1.15 [95%CI=0.56-2.37], p=0.698), or a recurrent seizure

Table 5. Adverse effects which led to treatment failure

Adverse effects which led to treatment failure[a]	LEV+VPA	Other duotherapy
Adverse effect categories based on the CTCAE v. 5.0	*Adverse effects, no. (%)*	*Adverse effects, no. (%)*
Gastrointestinal disorders	2 (4)	1 (4)
General and administration site conditions	5 (11)	2 (8)
Hepatobiliary disorders	2 (4)	0 (0)
Injury, poisoning and procedural complications	1 (2)	0 (0)
Investigations[1]	7 (15)	3 (13)
Metabolism and nutrition disorders	0 (0)	1 (4)
Nervous system disorders	16 (34)	11 (46)
Psychiatric disorders	8 (17)	2 (8)
Skin and subcutaneous tissue disorders	4 (9)	3 (13)
Unknown	2 (4)	1 (4)
Total number of adverse effects	47 (100)	24 (100)
Total number of patients who showed treatment failure due to adverse effects	35	15

[a]A more detailed description of all adverse effects, which led to treatment failure, can be found in the supplementary eTable 7; CTCAE=Common Terminology Criteria for Adverse Events; LEV+VPA=Levetiracetam combined with valproic acid; No.=Number of patients; [1]Includes adverse effects based on (laboratory) test results, for example decreased platelet count

(cause-specific aHR=0.99 [95%CI=0.65-1.51], p=0.968). However, patients on combinations with VPA had a significantly higher risk of experiencing treatment failure due to adverse effects (cause-specific aHR=10.10 [95%CI=1.31-78.04], p=0.027 [data not shown]).

Classification of evidence

This study provides Class III evidence that for glioma patients with uncontrolled seizures on AED monotherapy, LEV+VPA has better efficacy than other AED combinations.

Discussion

The aim of this retrospective observational cohort study was to evaluate the effectiveness of combined LEV+VPA compared to other AED duotherapy combinations including either LEV or VPA. We found that LEV+VPA has a similar level of toxicity compared to other duotherapies, but better efficacy. Greater efficacy of LEV+VPA was supported both by a lower risk for treatment failure due to uncontrolled seizures and a recurrent seizure. AED load at the moment of treatment failure was similar between the two groups, which suggests that the difference in efficacy between the two groups of duotherapy is not explained by a

discrepancy in dose escalation. This study showed as well that 1-year seizure freedom directly after AED duotherapy initiation is uncommon, since the cumulative incidence of a recurrent seizure at 12 months was equal to 74% (95%CI=68-79%) and 87% (95%CI=79-92%) for the combination of LEV+VPA and other AED duotherapies, respectively. Although polytherapy is generally considered as posing a higher risk for adverse effects,[25] this was not shown in our study as the cumulative incidence of treatment failure due to adverse effects at 6 months was equal to 10-11%, compared to 11-12% at 6 months in first-line monotherapy AED treatment in glioma patients,[5] and 10-14% in patients with non-brain tumor-related epilepsy at 6 months.[26, 27] Interestingly, other AED duotherapy combinations with LEV were tolerated very well compared to combinations with VPA, given only 2% (1/51) of the combinations with LEV showed treatment failure due to adverse effects. This implies that if patients on LEV+VPA experience intolerable adverse effects ascribed to VPA, replacement of VPA by another AED will probably be tolerated well.

First-line LEV has shown superior efficacy compared to VPA in the glioma population, with a similar level of toxicity, and should be considered as the preferred first-line AED in this population.[5] If patients fail to respond adequately to first-line LEV and need an add-on AED, VPA appears to be the preferred choice. Valproic acid may lead to hematologic toxicity, such as decreased platelet count, platelet dysfunction, and coagulation abnormalities. This particularly represents a concern for glioma patients who are on chemotherapy or in whom a surgical intervention is intended.[28] Since all of the other 15 unique AED duotherapy combinations with LEV and VPA were used by a limited number of patients, we could not draw conclusions about other possible synergistic effects. It is noteworthy that the duotherapy combination of LEV with lacosamide (LCM) has shown synergistic effects in preclinical studies and high efficacy in brain tumor patients.[29, 30] Still, about a quarter of patients on duotherapy show treatment failure due to uncontrolled seizures and need a third AED. Whether LEV+VPA is truly the most efficacious combination in glioma patients cannot be derived with certainty from our study. However, with a total number of up to 20 AEDs, ~200 possible duotherapy combinations can be made, it is extremely difficult to discover the most effective duotherapy combination.[31] Despite the general recommendation that polytherapy should only be considered when two attempts at monotherapy with AEDs have not resulted in seizure freedom,[32] two subsequent trials of monotherapy were found to be uncommon in our cohort (only 7% in this study). One of the most important reasons for the recommendation of a subsequent monotherapy trial instead of polytherapy is that AED monotherapy treatment is associated with fewer adverse effects in patients with epilepsy.[33] However, this has not been substantiated in the glioma population and given the suggested beneficial synergistic effect of the combination of LEV+VPA in glioma patients, reflected in a better efficacy, initiation of polytherapy if first-line monotherapy treatment fails seems to be an adequate treatment strategy in glioma patients. We believe our results have high external validity and can be generalized to other neuro-oncology clinics internationally.

Limitations

Considering patients may metabolize AEDs differently based on their pharmacogenetics, serum levels could have been a more reliable estimate than mean AED load. However, information on AED serum levels was not available, as they were rarely monitored by neuro-oncology professionals in clinical practice during follow-up.[34] In our analyses we only have adjusted for psychiatric comorbidities, while potentially other comorbidities may have contributed to treatment failure. Although valproic acid does not have any drug-drug interactions with levetiracetam, it does have interactions with other AEDs, such as phenytoin,[35] which might have contributed to treatment failure in the other AED duotherapy group. Only a third of glioma patients need AED duotherapy. This in combination with the relative rarity of the disease hinder to include a great number of patients, therefore limiting statistical power in this study.

Strengths

The inclusion of 236 patients on a specific duotherapy combination in such relatively rare disease as diffuse glioma can be called unique, given the high number of possible duotherapy combinations. Currently, there is a lack of randomized controlled trials (RCTs) and/or well-conducted observational studies on AED duotherapies in glioma patients. In our view the results of this manuscript are clinically very relevant and can help guide clinicians in their choice for AED duotherapy treatment. The results of our study are in line with previous data, which showed that the combination of LEV+VPA had a more favorable antiseizure effect compared to other AED duotherapy combinations. Only 40-41% of patients on LEV+VPA were not seizure free in the two previous studies,[12, 13] while at 12 months the cumulative incidence for a recurrent seizure was 74% for patients on LEV+VPA in our study. However, methodological issues were not taken into account, such as competing risks,[11] hampering adequate interpretation. In addition, both previous studies did not specifically define seizure freedom, i.e. it was unclear how long patients had to be free of seizures in order to be regarded as seizure free.[12, 13] We believe our results provide a reliable estimate of the risk for having a recurrent seizure if a patient starts with the combination of LEV+VPA.

Conclusion

To conclude, this retrospective observational cohort study suggests that LEV+VPA is more effective than other AED duotherapy combinations with either LEV or VPA, while the level of toxicity is similar. Duotherapy with LEV+VPA seems an appropriate choice in glioma patients if seizures are not adequately under control with AED monotherapy LEV or VPA.

Conflict of interest statement

All authors declare no competing interests.

Role of funding source

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Ethics committee approval

The institutional review board approved the study. If necessitated by the medical ethics committee of the institution (Amsterdam University Medical Center and Erasmus Medical Center), patients provided written informed consent.

Appendix 1. Author's contribution

Name	Location	Contribution
Pim B. van der Meer	Leiden University Medical Center, Leiden	Design, data collection, data-analysis, interpretation of results, intellectual content, wrote first and successive versions, and approved the final version. PBvdM had full access to all the data in the study and had final responsibility to submit for publication.
Linda Dirven	Leiden University Medical Center, Leiden; Haaglanden Medical Center, The Hague	Design, input in data-analysis, interpretation of results, intellectual content, critical revisions to the drafts of the paper, and approved the final version.
Marta Fiocco	Leiden University Medical Center, Leiden	Input in data-analysis, interpretation of results, intellectual content, critical revisions to the drafts of the paper, and approved the final version.
Maaike J. Vos	Haaglanden Medical Center, The Hague	Interpretation of results, intellectual content, critical revisions to the drafts of the paper, and approved the final version.
Mathilde C.M. Kouwenhoven	Amsterdam University Medical Centers, Location VUmc, Amsterdam	Interpretation of results, intellectual content, critical revisions to the drafts of the paper, and approved the final version.
Martin J. van den Bent	Erasmus Medical Center Cancer Institute, Rotterdam	Design, interpretation of results, intellectual content, critical revisions to the drafts of the paper, and approved the final version.
Martin J.B. Taphoorn	Leiden University Medical Center, Leiden; Haaglanden Medical Center, The Hague	Design, interpretation of results, intellectual content, critical revisions to the drafts of the paper, and approved the final version.
Johan A.F. Koekkoek	Leiden University Medical Center, Leiden; Haaglanden Medical Center, The Hague	Design, input in data-analysis, interpretation of results, intellectual content, critical revisions to the drafts of the paper, and approved the final version.

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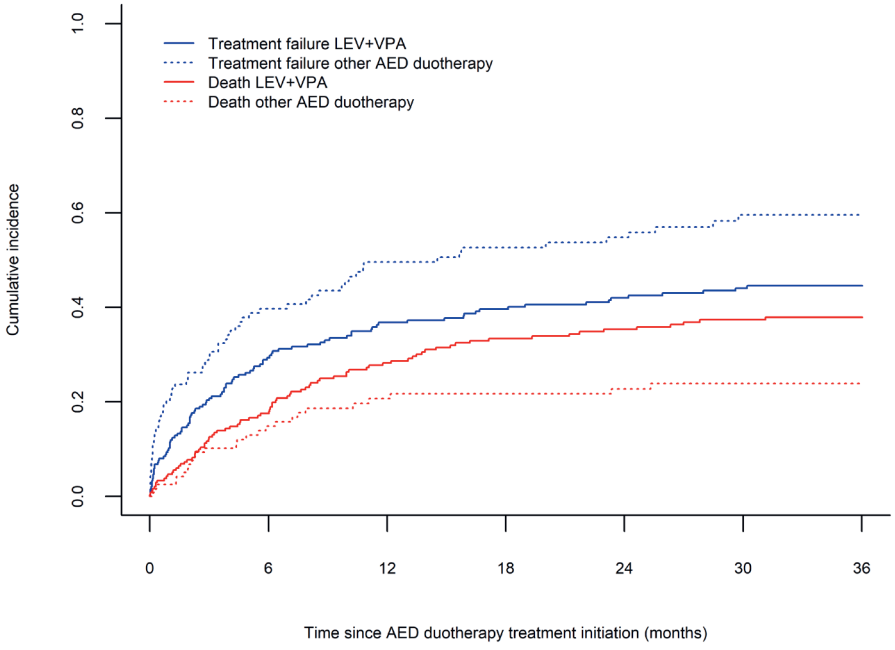
Supplementary material

eTable 1. List with defined daily dosages, as defined by the World Health Organisation, of antiepileptic drugs prescribed in this study.

Antiepileptic drug	Defined Daily dosage	Unit
Carbamazepine	1	g
Clobazam	20	mg
Clonazepam	8	mg
Gabapentin	1.8	g
Lacosamide	0.3	g
Lamotrigine	0.3	g
Levetiracetam	1.5	g
Oxcarbamazepine	1	g
Phenytoin	0.3	g
Topiramate	0.3	g
Valproic acid	1.5	g

G=gram, mg=milligram

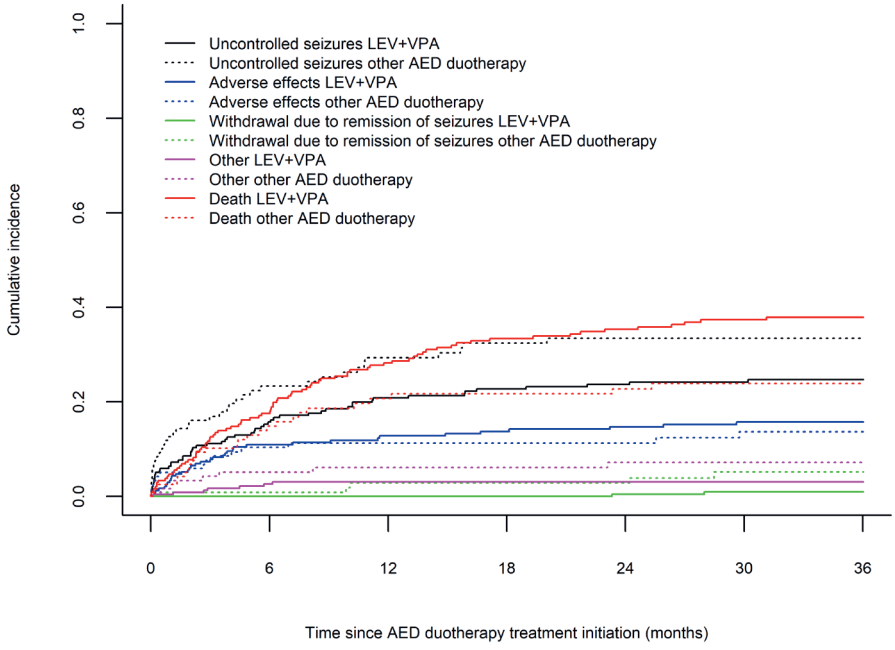
eTable 2. Number at risk, number censored, cumulative incidences for the competing events death and treatment failure for any reason, from antiepileptic drug duotherapy initiation: levetiracetam combined with valproic acid versus other antiepileptic drug duotherapy combinations.



Time in months	0	3	6	12	24	36	
No. at risk							
LEV+VPA, no.	236	150	115	74	47	0	
Other duotherapy, no.	119	68	48	29	21	0	
No. censored							
LEV+VPA, no.	0	9	14	16	17	54	
Other duotherapy, no.	0	4	8	11	12	28	
Event treatment failure for any reason							p=0.007
CIF (95%CI), LEV+VPA	0	21 (16-26)	29 (24-35)	37 (30-43)	42 (35-48)	45 (38-51)	
CIF (95%CI), other duotherapy	0	30 (22-38)	40 (31-49)	50 (40-59)	55 (45-64)	60 (49-68)	
Event death							p=0.024
CIF (95%CI), LEV+VPA	0	13 (9-17)	18 (13-23)	28 (22-34)	35 (29-42)	38 (31-44)	
CIF (95%CI), other duotherapy	0	10 (6-17)	15 (9-22)	21 (14-29)	23 (15-31)	24 (16-32)	

AED=Antiepileptic drug; CI=Confidence interval; CIF=Cumulative incidence function; LEV+VPA=Levetiracetam combined with valproic acid; No.=Number of patients

eTable 3. Number at risk, number censored, cumulative incidences for the competing events death and for specific reasons of treatment failure, from antiepileptic drug duotherapy initiation: levetiracetam combined with valproic acid versus other antiepileptic drug duotherapy combinations.



Time in months	0	3	6	12	24	36	
No. at risk							
LEV+VPA, no.	236	150	115	74	47	0	
Other duotherapy, no.	119	68	48	29	21	0	
No. censored							
LEV+VPA, no.	0	9	14	16	17	54	
Other duotherapy, no.	0	4	8	11	12	28	
Treatment failure							
Event uncontrolled seizures							p=0.069
CIF (95%CI), LEV+VPA	0	11 (8-16)	16 (11-21)	21 (16-26)	24 (18-29)	25 (19-31)	
CIF (95%CI), other duotherapy	0	17 (11-24)	23 (16-31)	29 (21-38)	33 (25-42)	33 (25-42)	
Event adverse effects							p=0.657
CIF (95%CI), LEV+VPA	0	8 (5-12)	11 (7-15)	13 (9-18)	15 (10-20)	16 (11-21)	
CIF (95%CI), other duotherapy	0	8 (4-13)	10 (6-17)	11 (6-18)	11 (6-18)	14 (8-21)	

Time in months	0	3	6	12	24	36	
No. at risk							
Event withdrawal due to remission of seizures[a]							p=0.020
CIF (95%CI), LEV+VPA	0	0 (-)	0 (-)	0 (-)	0 (0-3)	1 (0-3)	
CIF (95%CI), other duotherapy	0	1 (0-4)	1 (0-4)	3 (1-7)	3 (1-7)	5 (2-11)	
Event other reasons[b]							p=0.091
CIF (95%CI), LEV+VPA	0	2 (1-4)	3 (1-5)	3 (1-6)	3 (1-6)	3 (1-6)	
CIF (95%CI), other duotherapy	0	4 (2-9)	5 (2-10)	6 (3-12)	7 (3-13)	7 (3-13)	
Event death							p=0.024
CIF (95%CI), LEV+VPA	0	13 (9-17)	18 (13-23)	28 (22-34)	35 (29-42)	38 (31-44)	
CIF (95%CI), other duotherapy	0	10 (6-17)	15 (9-22)	21 (14-29)	23 (15-31)	24 (16-32)	

[a]Withdrawal due to remission of seizures was defined as discontinuation of the antiepileptic drug with consent of the medical doctor, regardless of the term being treated with the antiepileptic drug; [b]Other encompassed treatment failure due to unknown reasons (n=10), due to phenytoin not orally available in the hospital (n=1), due to possible interaction with temozolomide (n=1), due to possible interaction of clobazam with anesthesia (n=1); AED=Antiepileptic drug; LEV+VPA=Levetiracetam combined with valproic acid; No.=Number of patients

eTable 4. Unadjusted and adjusted cause specific hazard ratios of treatment failure due to uncontrolled seizures.

		Treatment failure due to uncontrolled seizures			
Parameter[a]		**uHR (95% CI)**	**p-value**	**aHR (95% CI)**	**p-value**
AED treatment	LEV+VPA (ref.)				
	Other duotherapy	1.50 (0.99-2.28	0.055	1.73 (1.10-2.73)	0.018*
Age		1.01 (0.99-1.02)	0.400	1.00 (0.98-1.02)	0.956
Tumor grade	2 (ref.)				
	3	0.72 (0.35-1.48)	0.373	0.89 (0.42-1.91)	0.767
	4	1.58 (0.99-2.51)	0.054	1.96 (1.02-3.77)	0.044*
Surgical resection	No (including biopsy, ref.)				
	Yes	1.02 (0.68-1.54)	0.915	1.09 (0.69-1.72)	0.711
Tumor involvement in the temporal lobe	No (ref.)				
	Yes	1.02 (0.67-1.54)	0.932	1.01 (0.65-1.56)	0.971
Karnofsky Performance Status	≥70 (ref.)				
	<70	1.18 (0.50-2.75)	0.706	1.05 (0.43-2.54)	0.918
Seizure type	Focal (ref.)				
	Focal to bilateral tonic clonic[b]	1.22 (0.77-1.93)	0.397	1.26 (0.79-2.03)	0.336

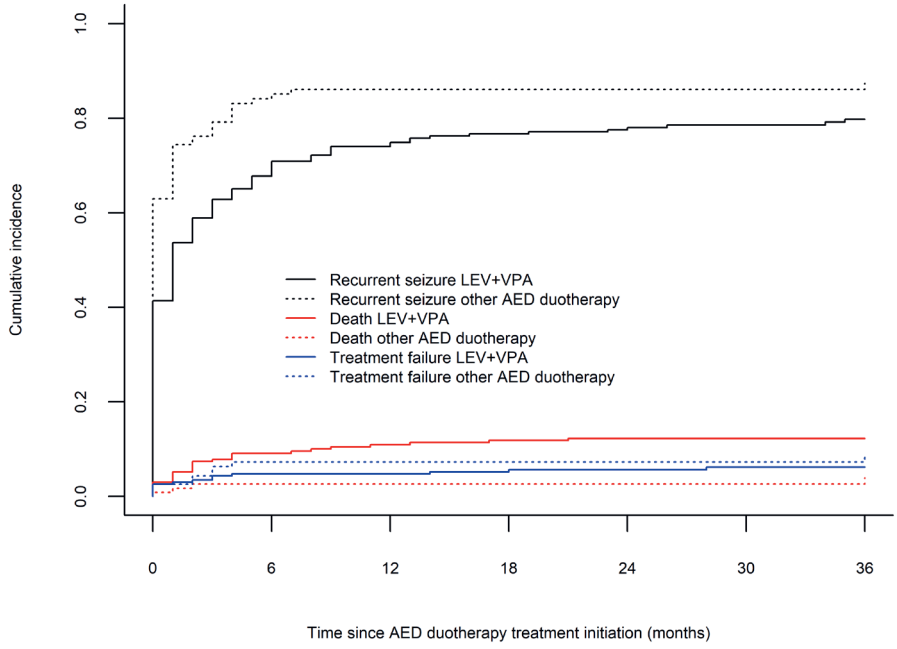
[a]Isocitrate dehydrogenase (IDH)-mutation, radiotherapy, and systemic therapy did not hold the proportionality assumption of the Cox regression model and were therefore stratified; [b]Patients had either solely focal to bilateral tonic-clonic seizures or both focal and focal to bilateral tonic-clonic seizures; *P-value <0.05; AED=Antiepileptic drug; aHR=Adjusted hazard ratio; CI=Confidence interval; LEV+VPA=Levetiracetam combined with valproic acid; uHR=Unadjusted hazard ratio

eTable 5. Unadjusted and adjusted cause specific hazard ratios of treatment failure due to adverse effects.

		Treatment failure due to adverse effects			
Parameter		**uHR (95% CI)**	**p-value**	**aHR (95% CI)**	**p-value**
AED treatment	LEV+VPA (ref.)				
	Other duotherapy	0.96 (0.52-1.75	0.886	0.88 (0.47-1.67)	0.703
Age		1.00 (0.98-1.02)	0.949	1.00 (0.98-1.02)	0.972
Sex	Male (ref.)				
	Female	1.34 (0.76-2.38)	0.316	1.32 (0.73-2.36)	0.357
Surgical resection	No (including biopsy, ref.)				
	Yes	0.84 (0.48-1.47)	0.544	0.80 (0.44-1.49)	0.486
Radiotherapy	No (ref.)				
	Yes	0.99 (0.56-1.74)	0.962	1.35 (0.60-3.03)	0.469
Systemic therapy	No (ref.)				
	Yes	0.81 (0.43-1.51)	0.506	0.78 (0.33-1.83)	0.562
Tumor involvement in the frontal lobe	No (ref.)				
	Yes	1.40 (0.73-2.67)	0.316	1.35 (0.69-2.67)	0.382
Karnofsky Performance Status	≥70 (ref.)				
	<70	1.16 (0.35-3.83)	0.805	1.11 (0.32-3.86)	0.874
History of a psychiatric disease[a]	No (ref.)				
	Yes	2.06 (0.88-4.85)	0.097	1.86 (0.77-4.47)	0.165
Seizure type	Focal (ref.)				
	Focal to bilateral tonic clonic[b]	1.05 (0.57-1.92)	0.887	1.12 (0.60-2.09)	0.717

[a]History of a psychiatric disease included depression, anxiety, or psychotic disorders; [b]Patients had either solely focal to bilateral tonic-clonic seizures or both focal and focal to bilateral tonic-clonic seizures; *P-value <0.05; AED=Antiepileptic drug; aHR=Adjusted hazard ratio; CI=Confidence interval; LEV+VPA=Levetiracetam combined with valproic acid; uHR=Unadjusted hazard ratio

eTable 6. Number at risk, number censored, number missing, cumulative incidences for the competing events death, treatment failure, and recurrent seizure, from antiepileptic drug duotherapy initiation: levetiracetam combined with valproic acid versus other antiepileptic drug duotherapy combination.



Time in months	**0**	**3**	**6**	**12**	**24**	**36**	
No. at risk							
LEV+VPA, no.	236	67	40	23	9	0	
Other duotherapy, no.	119	17	5	2	1	0	
No. censored							
LEV+VPA, no.	0	2	3	3	3	8	
Other duotherapy, no.	0	3	3	3	4	4	
No. missing values							
LEV+VPA, no.	4	4	4	4	4	4	
Other duotherapy, no.	3	3	3	3	3	3	
Event recurrent seizure							p<0.001
CIF (95%CI), LEV+VPA	0	59 (53-65)	68 (62-74)	74 (68-79)	78 (72-83)	80 (74-85)	
CIF (95%CI), other duotherapy	0	77 (68-83)	85 (77-91)	87 (79-92)	87 (79-92)	-	
Event death							p=0.017
CIF (95%CI), LEV+VPA	0	7 (4-11)	9 (6-13)	11 (7-15)	12 (8-17)	12 (8-17)	
CIF (95%CI), other duotherapy	0	3 (1-7)	3 (1-7)	4 (1-9)	4 (1-9)	-	

Time in months	0	3	6	12	24	36	
No. at risk							
Event treatment failure[a]							p=0.341
CIF (95%CI), LEV+VPA	0	4 (2-7)	5 (3-8)	5 (3-8)	6 (3-9)	6 (4-10)	
CIF (95%CI), other duotherapy	0	4 (2-10)	7 (3-13)	7 (3-13)	7 (3-13)	-	

[a]Patients who experienced treatment failure (due to adverse effects, withdrawal due to remission of seizures, or other reasons) before experiencing their recurrent seizure, can no longer experience a recurrent seizure on their first-line monotherapy levetiracetam or valproic acid, and therefore treatment failure was handled as competing risk; AED=Antiepileptic drug; CI=Confidence interval; CIF=Cumulative incidence function; LEV=Levetiracetam; No.=Number of patients; VPA=Valproic acid

eTable 7. Adverse effects which led to treatment failure in detail.

Adverse Effects According to the CTCAE 5.0	Levetiracetam + Valproic acid							Other antiepileptic drug duotherapy						
	Grade, no.				Improved, no.[a]			Grade, no.				Improved, no.[a]		
	1,2	3,4	?	Total	Yes	No	?	1,2	3,4	?	Total	Yes	No	?
Gastrointestinal disorders														
Dyspepsia	-	-	-	-	-	-	-	1	-	-	1	1	-	-
Nausea	1	-	-	1	1	-	-	-	-	-	-	-	-	-
Pancreatitis	-	1	-	1	1	-	-	-	-	-	-	-	-	-
Total	1	1	-	2	2	-	-	1	-	-	1	1	-	-
General and administration site conditions														
Clinical deterioration	-	1	-	1	-	1	-	-	-	-	-	-	-	-
Fatigue	3	-	-	3	3	-	-	1	-	-	1	1	-	-
Gait disturbance	1	-	-	1	1	-	-	1	-	-	1	-	-	1
Total	4	1	-	5	4	1	-	2	-	-	2	1	-	1
Hepatobiliary disorders														
Hepatic failure	-	2	-	2	1	-	1	-	-	-	-	-	-	-
Total	-	2	-	2	1	-	1	-	-	-	-	-	-	-
Injury, poisoning and procedural complications														
Fall	1	-	-	1	-	1	-	-	-	-	-	-	-	-
Total	1	-	-	1	-	1	-	-	-	-	-	-	-	-
Investigations														
Ammonia increased	1	-	-	1	-	-	1	-	-	-	-	-	-	-
Platelet count decreased	2	2	-	4	3	-	1	-	1	1	2	-	2	-
Weight gain	1	-	1	2	1	-	1	1	-	-	1	-	-	1
Total	4	2	1	7	4	-	3	1	1	1	3	-	2	1
Metabolism and nutrition disorders														
Hyponatremia	-	-	-	-	-	-	-	-	-	1	1	1	-	-
Total	-	-	-	-	-	-	-	-	-	1	1	1	-	-
Nervous system disorders														
Bradyphrenia	-	-	-	-	-	-	-	1	-	-	1	-	-	1
Concentration impairment	-	-	-	-	-	-	-	-	1	-	1	1	-	-
Dizziness	1	-	-	1	-	1	-	-	-	-	-	-	-	-
Dysarthria	-	-	-	-	-	-	-	1	-	-	1	-	1	-
Encephalopathy	1	1	-	2	2	-	-	-	1	-	1	1	-	-
Headache	2	-	-	2	1	1	-	1	-	-	1	1	-	-
Lethargy	1	-	-	1	1	-	-	-	-	-	-	-	-	-
Memory impairment	-	-	-	-	-	-	-	-	1	-	1	1	-	-

Adverse Effects According to the CTCAE 5.0	Levetiracetam + Valproic acid							Other antiepileptic drug duotherapy						
	Grade, no.				Improved, no.[a]			Grade, no.				Improved, no.[a]		
	1,2	3,4	?	Total	Yes	No	?	1,2	3,4	?	Total	Yes	No	?
Presyncope	-	-	-	-	-	-	-	1	-	-	1	1	-	-
Somnolence	2	-	-	2	2	-	-	3	-	-	3	1	-	2
Tremor	8	-	-	8	5	1	2	1	-	-	1	1	-	-
Total	15	1	-	16	11	3	2	8	3	-	11	7	1	3
Psychiatric disorders														
Agitation	2	-	-	2	1	-	1	-	-	-	-	-	-	-
Anxiety	-	-	-	-	-	-	-	1	1	-	2	-	2	-
Depression	1	2	-	3	3	-	-	-	-	-	-	-	-	-
Hallucinations	-	1	-	1	1	-	-	-	-	-	-	-	-	-
Irritability	1	-	-	1	1	-	-	-	-	-	-	-	-	-
Suicidal ideation	-	1	-	1	1	-	-	-	-	-	-	-	-	-
Total	4	4	-	8	7	-	1	1	1	-	2	-	2	-
Skin and subcutaneous tissue disorders														
Alopecia	1	-	-	1	-	-	1	-	-	-	-	-	-	-
Pruritis	1	-	-	1	1	-	-	-	-	-	-	-	-	-
Rash	1	-	1	2	1	-	1	2	-	1	3	3	-	-
Total	3	-	1	4	2	-	2	2	-	1	3	3	-	-
Unknown														
Unknown	1	-	1	2	2	-	-	-	-	1	1	1	-	-
Total	1	-	1	2	2	-	-	-	-	1	1	1	-	-
Total all adverse effects	33	11	3	47	33	5	9	15	5	4	24	14	5	5

?=Unknown; [a]=Improvement after discontinuation of the current therapy with levetiracetam + valproic acid or other antiseizure medication duotherapy; CTCAE=Common Terminology Criteria for Adverse Events; No.=Number of patients